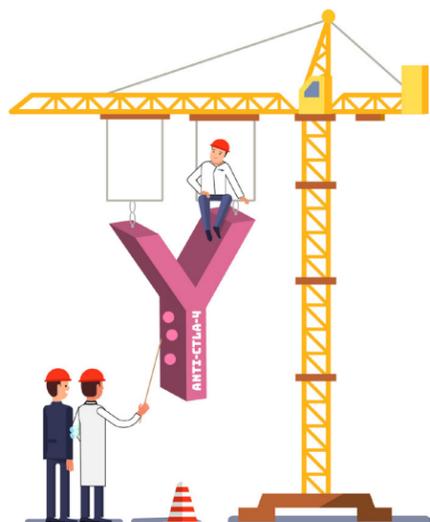


## Agenus' Next-Gen anti-CTLA-4 (AGEN1181) Can this be a breakthrough cancer treatment?

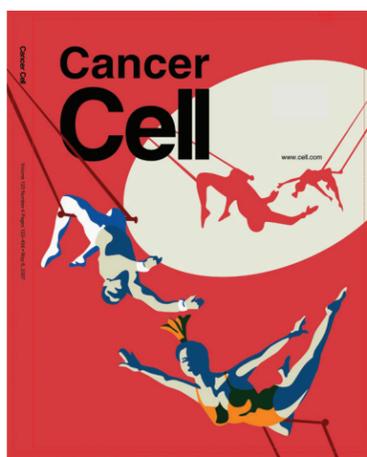


CTLA-4 (cytotoxic T-lymphocyte antigen-4) is a crucial target for unlocking the immune system's ability to kill cancer cells. In 2018, the Nobel Prize in Physiology or Medicine was awarded to Jim Allison for his efforts in establishing CTLA-4 as a cancer immunotherapy target. A first generation commercial anti-CTLA-4 antibody has achieved unprecedented success in treating and even curing a small proportion of patients. AGEN1181 represents an important next-generation breakthrough with its potential to treat patients with cancer. **AGEN1181 has generated considerable excitement among key opinion leaders, and we expect to dose our first patient in the next several weeks.**

AGEN1181, with its potential for enhanced immune activation and tumor fighting abilities, was specifically designed to boost cancer killing immune cells and defeat cells that block the activity of these cancer killing cells.

Hence, AGEN1181 has the potential to be effective in a higher proportion of patients with cancer than first generation CTLA-4 blocking agents. In addition, AGEN1181 may significantly expand the commercial potential of our anti-PD-1 antibody when used in combination. This could differentiate the Agenus I-O portfolio from others including some of the leaders in the field.

### A Breakthrough Discovery by Agenus Scientists Led to the Development of AGEN1181



In 2018, Agenus [scientists revealed](#) a novel mechanism of action for certain type of antibodies used in cancer immunotherapy, including those targeting CTLA-4. By modifying a key region of the antibody known as the "Fc region", Agenus' discovery enabled the design of antibodies that could significantly enhance functionality and antitumor immunity. This discovery was published in the high-impact scientific journal [Cancer Cell](#).

Based on this finding, Agenus scientists modified the Fc region of Agenus' anti-CTLA-4 antibody to significantly improve its biological activity. This led to enhancement in immune responses, as seen in a range of pre-clinical studies. In these studies, the "Fc-engineered" antibody significantly improved the cross-talk between antigen presenting cells and T cells. In cancer immunotherapy, such an interaction is critical to mount effective immune responses against the tumor. Agenus' team has applied this discovery to other mono- and multi-specific antibodies in its pipeline, leading to the development of other Fc-engineered antibodies, now in pre-clinical studies.

### AGEN1181 Has Key Advantages Over First-Generation Anti-CTLA-4 Antibodies

Researchers have explored CTLA-4 biology and associated immunotherapies for years with only incremental progress in our mechanistic understanding of the target and drug design. With Fc-based antibody engineering, we believe that Agenus has uncovered a way to significantly improve anti-CTLA-4 antibody function. AGEN1181 is designed to have several advantages over first-generation anti-CTLA-4 antibodies. These include:

- 1 Ability to induce enhanced T cell priming via the engineered Fc region. T cell priming is a crucial step in generating potent immune responses against cancer.
- 2 Increased potential to deplete intratumoral regulatory T cells, which represent a significant barrier to successful anti-cancer immune responses.
- 3 Better combination potential with other antitumor or immunomodulatory antibodies, vaccines, and targeted therapies.
- 4 Potential for therapeutic benefit to a wider patient population, including the estimated 40% of patients who are unlikely to fully benefit from to first generation CTLA-4 therapies due to a genetic predisposition.
- 5 Potential for improved safety profile that may enable flexible dosing options.

### AGEN1181 Adds Value to Agenus' Rationally Designed Pipeline

In addition to our anti-PD-1 and first-generation anti-CTLA-4 therapies, Agenus has developed a broad pipeline designed to attack cancer from multiple angles. **As a next-generation molecule with enhanced function, AGEN1181 has been designed to be a best-in-class anti-CTLA-4 antibody that may represent an optimal combination partner for a range of other therapeutic interventions** – including other antibodies, vaccines or cell therapy – across expanded cancer indications. Based on the expected mechanistic advantages outlined above, we anticipate AGEN1181 to enhance the therapeutic benefit possible from combination studies.

**We expect to treat our first patient with AGEN1181 in the coming weeks. We also expect to initiate combination trials with AGEN1181 during this year.**

Forward-Looking Statements: This Agenus News Brief includes forward-looking statements that are made pursuant to the safe harbor provisions of the federal securities laws, including statements regarding the anticipated benefits of AGEN1181 compared to first generation antibodies, as well as clinical development plans and timelines. These statements are subject to risks and uncertainties, including those described in our SEC filings. Please refer to [this link](#) for more details.